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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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22850	7590	04/25/2006	EXAMINER	
OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314			LU, FRANK WEI MIN	
			ART UNIT	PAPER NUMBER

1634

DATE MAILED: 04/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/996,591	Applicant(s) KONDOW ET AL.	
	Examiner Frank W Lu	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 February 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 and 26-36 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 and 26-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 November 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on February 23, 2006 has been entered. The claims pending in this application are claims 1-10 and 26-35. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the response filed on February 23, 2006.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-4, 7-10, 26-29, and 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parce *et al.*, (US Patent No. 6,613,513, priority date; February 23, 1999) in view of Innis *et al.*, (US Patent No. 5,075,216, published on December 24, 1991).

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Regarding claim 1, Parce *et al.*, teach a method for determining a nucleotide sequence of a single nucleic acid molecule, which comprises: (a) immobilizing a nucleic acid molecule onto the surface of a solid (ie., a fixed location within a microscale channel); (b) annealing a primer to said nucleic acid molecule, wherein said primer has a sequence complementary to a part of a sequence of the nucleic acid molecule; (c) providing a solution which contains a DNA polymerase and only one type of dye-labeled dNTP, where N is A, T or U, G or C, or an RNA polymerase and only one type of dye-labeled NTP, where N is A, U, G or C, to said immobilized nucleic acid molecule, and allowing the dye-labeled dNTP or NTP to react with the 3' end of said primer, whereby the dye-labeled dNTP or NTP, which forms a base-pair with a base in the nucleic acid molecule at a position where the dye-labeled dNTP or NTP reacts with the 3' end of said primer and, is bound to the primer by action of the polymerase wherein the dye-labeled dNTP or NTP is labeled with dye thereby permitting the incorporation of a sequential dNTP or NTP to the 3' end of the dye-labeled dNTP or NTP (the dye-labeled dNTP or NTP taught by Parce *et al.*, has this ability); (d) detecting a bound, dye-labeled dNTP or NTP; (e) disrupting the dye molecule of the bound, dye-labeled dNTP or NTP; (e) repeating (c) to (e) while changing the type of dye-labeled dNTP or NTP in turn, to sequentially bind dNTPs or NTPs which forms a base-pair with the nucleotides of the nucleic acid molecule; and (g) determining a nucleotide sequence of the nucleic acid molecule based on the types of the sequentially bound dNTPs or NTPs (see claims 1-26 in columns 37-39 and columns 2-4).

Regarding claim 26, Parce *et al.*, teach a method for determining a nucleotide sequence of a single nucleic acid molecule, which comprises: (a) immobilizing a primer onto the surface of a solid (ie., a fixed location within a microscale channel), wherein the primer comprises a

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sequence complementary to a part of a sequence in the nucleic acid molecule; (b) annealing a nucleic acid molecule to the immobilized primer; (c) providing a solution which contains a DNA polymerase and only one type of dye-labeled dNTP, where N is A, T or U, G or C, or an RNA polymerase and only one type of dye-labeled NTP, where N is A, U, G or C, to said immobilized nucleic acid molecule, and allowing the dye-labeled dNTP or NTP to react with the 3' end of said primer, whereby the dye-labeled dNTP or NTP, which forms a base-pair with a base in the nucleic acid molecule at a position where the dye-labeled dNTP or NTP reacts with the 3' end of said primer and is bound to the primer by action of the polymerase wherein the dye-labeled dNTP or NTP is labeled with dye thereby permitting the incorporation of a sequential dNTP or NTP to the 3' end of the dye-labeled dNTP or NTP (the dye-labeled dNTP or NTP taught by Parce *et al.*, has this ability); (d) detecting a bound, dye-labeled dNTP or NTP; (e) disrupting the dye molecule of the bound, dye-labeled dNTP or NTP; (e) repeating (c) to (e) while changing the type of dye-labeled dNTP or NTP in turn, to sequentially bind dNTPs or NTPs which forms a base-pair with the nucleotides of the nucleic acid molecule; and (g) determining a nucleotide sequence of the nucleic acid molecule based on the types of the sequentially bound dNTPs or NTPs (see claims 1-26 in columns 37-39 and columns 2-4).

Regarding claims 2 and 27, Parce *et al.*, teach said surface of a solid is the inner wall of a capillary (ie., a microscale channel) (see column 4, second paragraph).

Regarding claims 3 and 28, Parce *et al.*, teach optically detecting the dye molecule of said dye-labeled dNTP or NTP (see claims 3-5 in columns 37 and 38).

Regarding claims 4 and 29, Parce *et al.*, teach exciting dye molecules by irradiation of a laser beam and detecting a fluorescent signal (see columns 33 and 35, specially see column 34, lines 52-64).

Regarding claims 7-9 and 32-34, Parce *et al.*, teach that said dye is a fluorescent dye. wherein said dye-labeled dNTP or NTP is labeled with rhodamine, tetramethyl rhodamine (fluorescein) Rhodamine 6G, fluorescein isothiocyanate, or 4-fluoro-7-nitro-berlzo-furazon (Texas Red) (see column 5).

Regarding claims 10 and 35, Parce *et al.*, teach that said dNTP or NTP is each labeled with the same dye (see column 15, lines 27-35).

Parce *et al.*, do not disclose that said solution consists of a droplet in which an aqueous solution containing said dye-labeled dNTP or NTP is entrapped within a hydrophobic liquid as recited in claims 1 and 26.

Regarding claims 1 and 26, since Innis *et al.*, teach to overlay mineral oil onto an aqueous solution containing dNTPs in sequencing reactions which are performed in 96-well microtiter plates (see column 12, second paragraph), Innis *et al.*, disclose that a solution consists of a droplet in which an aqueous solution containing said dNTPs is entrapped within a hydrophobic liquid (ie., mineral oil).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 1 or 26 wherein said solution consists of a droplet in which an aqueous solution containing said dye-labeled dNTP or NTP is entrapped within a hydrophobic liquid (ie., mineral oil) in view of the patents of Parce *et al.*, and Innis *et al.*. One having ordinary skill in the art would have been

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motivated to do so because Innis *et al.*, suggest that overlaying mineral oil onto an aqueous solution containing dNTPs would prevent evaporation of the aqueous solution during the sequencing reaction (see column 12, second paragraph). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to overlay mineral oil onto an aqueous solution containing dye-labeled dNTPs in order to prevent evaporation of the aqueous solution during the sequencing reaction.

Response to Arguments

In page 2, second paragraph bridging to page 3, fourth paragraph of applicant's remarks, applicant argues that: (1) "[I]n Parce, the method involves a chain terminating nucleotide moiety, see the Abstract ('chain terminating nucleotides), col. 9, lines 39-41 ('*primer strands are terminated by the addition of a nucleotide comprising a blocking group*'), col. 11, lines 50-56 ('*The chain terminating nucleotides typically contain a blocking group on the 3' OH. A 'blocking group' typically prevents addition of a nucleotide to the 3' terminus ...*') These types of chain terminating nucleotides are known (see the attached paper by Sanger et al (1977) Proc. Natl. Acad. Sci. USA 74:5463-5467) and are different from those used in the claims. The claimed methods employ a dye-labeled dNTP or NTP labeled in such a way so as to permit further elongation by incorporating additional dNTPs or NTPs (labeled or un-labeled) at the 3' position of the dye-labeled dNTP or NTP. In Parce, the nucleotides are blocked at the 3' position (see citations above) and may be fluorescently labeled (col. 15, lines 28-35). Contrary to the conclusion stated on page 3 of the Office Action (i.e., 'the dye-labeled dNTP or NTP taught by *Parce et al.*, has this ability'), the *Parce* nucleotides used are clearly chain terminating nucleotides. Before repeating the chain elongation, the blocking group must be removed (see,

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e.g., col. 14, lines 22-30). In contrast, in the claimed method, the dye-labeled dNTP or NTP is not blocked at the 3' position (permitting the addition of further nucleotides) and therefore no removal of a blocking moiety is needed"; (2) "[Innis is relied upon to allege that it would have been obvious to use mineral oil to overlay a solution. However, Innis does not describe the types of dye-labeled nucleotides used in the claimed method nor would one have modified the Parce method to use the types of dye-labeled nucleotides in the claims based on Innis"; and (3) "while Innis teach overlaying mineral oil to prevent evaporation, this is not the same as *entrapping* a solution within a hydrophobic liquid. The introduction of the reaction solution containing polymerase, nucleotides etc, in the hydrophobic liquid facilitates the reaction in terms of limiting the reaction to only sites where the nucleotide is immobilized and inhibiting unreacted nucleotides from being adsorbed in inappropriate places, which is disadvantageous in terms of having to wash away unreacted nucleotides. Furthermore, by entrapping the reaction solution (not simply overlaying as in Innis) background signals can be greatly decreased".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, although Parce et al., teach to use a nucleotide comprising a blocking group and provide reversible chain-termination for nucleic acid sequencing, since the claims do not require the incorporation of a sequential dNTP or NTP to the 3' end of the dye-labeled dNTP or NTP before disrupting the dye molecule of the bound, dye-labeled dNTP or NTP and Parce et al., teach that the blocking group is removed to allow addition of another nucleotide (see column 11), Parce et al., disclose that the dye-labeled dNTP or NTP is labeled with dye thereby permitting the incorporation of a sequential dNTP or NTP to the 3' end of the dye-labeled dNTP or NTP as recited in claims 1 and 26. Second, Parce et al., also teach other

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different sequencing methods. One of sequencing methods is sequencing by photobleaching. In this sequencing method, a fluorescently labeled nucleotide is detected as it is added to a growing nucleic acid chain, e.g., a primer that is hybridized to a template and fluorescently labeled nucleotides are photobleached after incorporation to reduce the signal level and increase the template nucleic acid read length wherein photobleaching destroys or reduces the fluorescence of the at least one of the one or more fluorescently labeled nucleotides to an acceptable level without removing the labeled nucleotide(s) from the extended primer (see columns 18 and 19, and claim 1 in column 37). Since the claims do not require to disrupt the structure of the dye molecule and sequencing by photobleaching does not removing the labeled nucleotide(s) from the extended primer, Parce *et al.*, disclose that the dye-labeled dNTP or NTP is labeled with dye thereby permitting the incorporation of a sequential dNTP or NTP to the 3' end of the dye-labeled dNTP or NTP as recited in claims 1 and 26. Third, Innis *et al.*, do describe the types of dye-labeled nucleotides used in the claimed method since Innis *et al.*, teach dNTP labeled with a fluorescent molecule (see column 15, claim 12). Fourth, since Innis *et al.*, teach to overlay mineral oil onto an aqueous solution containing dNTPs in sequencing reactions which are performed in 96-well microtiter plates (see column 12, second paragraph), Innis *et al.*, disclose that a solution consists of a droplet in which an aqueous solution containing said dNTPs is entrapped within a hydrophobic liquid (ie., mineral oil). Fifth, the claims do not require inhibiting unreacted nucleotides from being adsorbed in inappropriate places and greatly decreasing background signals by entrapping the reaction solution as argued by applicant.

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4. Claims 5 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parce *et al.*, in view of Innis *et al.*, as applied to claims 1-4, 7-10, 26-29, and 32-35 above, and further in view of Mathies *et al.*, (US Patent No.5,091,652, published on February 25, 1992).

The teachings of Parce *et al.*, and Innis *et al.*, have been summarized previously, *supra*.

Parce *et al.*, and Innis *et al.*, do not disclose to detect fluorescence signals using a confocal fluorescence microscope system as recited in claims 5 and 30. However, Parce *et al.*, teach that, in their method, fluorescence signal is detected using a microscope objective of varying power, field diameter, and focal length or CCD (see column 34, lines 30-51).

Mathies *et al.*, teach to detect fluorescence signals using a confocal fluorescence microscope system (i.e., a laser excited confocal microscope fluorescence scanner) (see abstract and Figure 1).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 5 or 30 using a confocal fluorescence microscope system in view of the patents of Parce *et al.*, Innis *et al.*, and Mathies *et al.*. One having ordinary skill in the art would have been motivated to do so because Mathies *et al.*, have successfully used a confocal fluorescence microscope system to detect fluorescence signals and the simple replacement of one well known fluorescence detection device (i.e., a microscope objective of varying power, field diameter, and focal length or CCD taught by Parce *et al.*,) from another well known fluorescence detection device (i.e., a confocal fluorescence microscope system taught by Mathies *et al.*,) during the process of detecting fluorescence signals would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made

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because the fluorescence detection device taught by Parce *et al.*, and the fluorescence detection device taught by Mathies *et al.*, are used for the same purpose (ie., detecting fluorescence signals).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements in such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 3, last paragraph bridging to page 4, first paragraph of applicant's remarks, applicant argues "[M]athies is relied upon to provide the use of confocal fluorescence microscopy to detect fluorescent signals. Matheis does not suggest replacing the chain terminating nucleotide in Parce nor entrapping the reaction solution. Therefore, the combination of these publications provides no description nor reasonable suggestion to employ the dye-labeled dNTP or NTP coupled with entrapment with hydrophobic liquid as claimed".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection because the combination of Parce *et al.*, and Innis *et al.*, do teach dye-labeled dNTP or NTP coupled with entrapment with hydrophobic liquid (see above arguments related to the rejection under 35 U.S.C. 103(a) over Parce *et al.*, in view of Innis *et al.*).

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5. Claims 6 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parce *et al.*, in view of Innis *et al.*, as applied to claims 1-4, 7-10, 26-29, and 32-35 above, and further in view of Anazawa *et al.*, (US Patent No.6,242,193, priority date: July 30, 1999).

The teachings of Parce *et al.*, and Innis *et al.*, have been summarized previously, *supra*.

Parce *et al.*, and Innis *et al.*, do not disclose that said disrupting the dye molecules in (e) comprises irradiating with a laser beam stronger than the laser beam in (d) as recited in claims 6 and 31. However, Parce *et al.*, teach disrupting the dye molecules using different methods such as photobleaching (see columns 2-4).

Anazawa *et al.*, teach detecting and disrupting the dye molecules using a laser beam (see abstract). Since the intensity of laser used for disrupting the dye molecules must stranger than the intensity of laser used for detecting the dye molecules, Anazawa *et al.*, disclose claims 6 and 31.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 6 or 31 wherein said disrupting the dye molecules in (e) comprises irradiating with a laser beam stronger than the laser beam in (d) in view of the patents of Parce *et al.*, Innis *et al.*, and Anazawa *et al.*. One having ordinary skill in the art would have been motivated to do so because Anazawa *et al.*, have successfully used a laser beam for detecting and disrupting the dye molecules and the simple replacement of one well known fluorescence disrupting method (i.e., the disrupting method taught by Parce *et al.*,) from another well known fluorescence disrupting method (i.e., the disrupting method taught by Anazawa *et al.*, using a laser beam) during the process of performing the method recited in claim 6 or 31, would have been, in the absence of convincing

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evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the method taught by Parce *et al.*, and the method taught by Anazawa *et al.*, are used for the same purpose (ie., disrupting the dye molecules).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements in such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 4, second paragraph of applicant's remarks, applicant argues that "[A]nazawa describe a primer extension reaction using DNA polymerase and four types of NTPS, each of which are differentially labeled (see column 6, lines 27-33 of Anazawa). Anazawa is relied upon to provide the use of lasers to disrupt the dye molecule. Anazawa does not suggest replacing the chain terminating nucleotide in Parce nor entrapping the reaction solution. Therefore, the combination of these publications provides no description nor reasonable suggestion to employ the dye-labeled dNTP or NTP coupled with entrapment with hydrophobic liquid as claimed.

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection because the combination of Parce *et al.*, and Innis *et al.*, do teach dye-labeled dNTP or NTP coupled with entrapment with hydrophobic liquid (see above

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arguments related to the rejection under 35 U.S.C. 103(a) over Parce *et al.*, in view of Innis *et al.*).

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. No claim is allowed.

8. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746.

The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Frank Lu
Primary Examiner
April 24, 2006



FRANK LU
PRIMARY EXAMINER